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http://dx.doi.org/10.1289/ehp.1408407

Received: 12 March 2014
Accepted: 19 November 2014
Advance Publication: 21 November 2014

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Associations of Plasma Concentrations of Dichlorodiphenyldichloroethylene and Polychlorinated Biphenyls with Prostate Cancer: A Case–Control Study in Guadeloupe (French West Indies)

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Running head: DDE and PCB153 exposure and prostate cancer

Acknowledgments: This work was supported by the French National Health Directorate. E Emeville is supported by a Ph.D. fellowship from the Ligue Nationale Contre le Cancer. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing financial interests: The authors declare they have no actual or potential competing financial interests.

Abstract

Background: Long-term exposure to persistent pollutants with hormonal properties (endocrine-disrupting chemicals, EDCs) may contribute to the risk of prostate cancer (PCa). However, epidemiological evidence remains limited.

Objectives: We investigated the relationship between PCa and plasma concentrations of universally widespread pollutants, in particular p,p'-dichlorodiphenyl dichloroethene (DDE) and the non-dioxin like polychlorinated biphenyl congener 153 (PCB153).

Methods and Findings: We evaluated before treatment 576 men with newly diagnosed PCa and 655 controls in Guadeloupe (French West Indies). Exposure was analyzed according to case-control status. Associations were assessed by unconditional logistic regression analysis, controlling for confounding factors. Missing data were handled by multiple imputation. We estimated a significant positive association between DDE and PCa (adjusted odds ratio [OR] 1.53; 95% CI 1.02, 2.30 for the highest versus lowest quintile of exposure; $P_{Trend} = 0.01$). PCB153 was inversely associated with PCa (OR 0.30; 95% CI 0.19, 0.47 for the highest versus lowest quintile of exposure values; $P_{Trend} <0.001$). Also, PCB153 was more strongly associated to low-grade than high grade PCa.

Conclusions: Associations of PCa with DDE and PCB153 were in opposite directions. This may reflect differences in the mechanisms of action of these EDCs, and although our findings need to be replicated in other populations, they are consistent with complex effects of EDCs on human health.

Introduction

Prostate cancer (PCa) is the second most common non-cutaneous cancer among men worldwide and the leading non-cutaneous cancer among men in developed countries (Center et al. 2012). Little is known about the risk factors associated with this cancer: advancing age, ethnic origins, and a family history of PCa are the only established risk factors (Damber 2008; Hsing and Chokkalingam 2006). Many lifestyle-related risk factors, including westernization of eating habits and environmental chemical pollution, have been implicated, but their true roles in the etiology of PCa remain unclear (Damber 2008; Hsing and Chokkalingam 2006).

The effects of exposure to synthetic chemicals with hormonal properties in the environment, also called endocrine disruptors (EDCs), on prostate cancer development are also matters of debate (Diamanti-Kandarakis et al. 2009; Prins 2008; WHO 2013). Models of PCa are not available for regulatory testing. This makes the identification of prostatic hormonal carcinogens very difficult and forces researchers to rely on epidemiological studies. However, epidemiological evidence remains limited (Soto and Sonnenschein 2010).

Persistent organic pollutants, including p,p'-dichlorodiphenyldichloroethene (DDE, the major and most stable metabolite of dichlorodiphenyltrichloroethane, DDT) and Polychlorinated biphenyls (PCBs), have attracted attention because of their widespread presence both in the environment and in human beings, and their ability to interfere with hormone-regulated processes (Kelce et al. 1995; Plísková et al. 2005). Several epidemiological studies have investigated relationships between human exposure to DDE and PCBs, determined by blood measurement, and PCa, but most of them found no association (Aronson et al. 2010; Ritchie et al. 2003, 2005; Sawada et al. 2010). One study in U.S. that included 65 PCa cases and 1920

noncases reported a positive but not significant association with prevalent prostate cancer risk(Xu et al. 2010).

In a population-based case-control study of incident PCa patients and control subjects in the general population in Guadeloupe (French West Indies), environmental exposure to the estrogenic insecticide chlordecone was positively associated with PCa (Multigner et al. 2010). Here, we report continuation of this study with a more detailed investigation of associations of DDE and PCBs with PCa.

Methods

Study population

This study took place in Guadeloupe (French West Indies), a Caribbean archipelago, where most of the inhabitants are of African descent. The study included 709 consecutive incident cases of histologically confirmed PCa and 723 controls without PCa. Details of the selection of cases and controls have been described elsewhere (Multigner et al. 2010). Briefly, cases patients were recruited among subjects attending public and private urology clinics with a recruitment area covering the entire territory of the Guadeloupe Archipelago. Controls were recruited from men participating in a free systematic health screening program open to the general population: each year, a random population sample selected in accordance with the sex and age distribution of the general population was invited to participate in the program. Consecutive men aged 45 or older were then invited to participate as controls in our case-control study of PCa, with selection according to the approximate age distribution of PCa diagnosis in Guadeloupe. Inclusion criteria for both cases and controls were current residence in Guadeloupe, both parents born on any Caribbean island with a population of predominantly African descent, and no hormone

treatments or use of any other drugs known to influence the hypothalamic-pituitary-gonadal-adrenal axis (including inhibitors of 5α-reductase). Additional inclusion criteria for controls were normal findings upon digital rectal examination and total plasma PSA concentration no higher than the 75th percentile for the corresponding age group of African American men without clinical evidence of PCa (Morgan et al. 1996). Trained nurses obtained information for both patients and controls. Case patients were interviewed within two months of diagnosis, prior to receiving any kind of treatment. All subjects were interviewed in person to obtain information about their age (years), Caribbean origin (French West Indies, Haiti or Dominica), education (primary, secondary, high school and higher), weight and height allowing the calculation of body mass index (BMI, kg/m^2), waist and hip circumference allowing the calculation of waist-to-hip-ratio (≤ 0.95, > 0.95), smoking (never, former or current), alcohol consumption (never, former or current), diabetes type 2 (no, yes), past residence in Western countries (no, yes), history of PSA screening (within the last 5 years: no, yes), and family history of PCa (first degree relatives: no, yes, not known). Participants were also asked to provide a blood sample between 8.00 and 10.00 a.m. after overnight fasting. The study was approved by the Guadeloupean ethics committee for studies involving human subjects. Each participant provided written informed consent.

Laboratory assays

A high-resolution gas chromatograph (Thermo Quest Trace 2000, Milan, Italy) equipped with a Ni63 electron capture detection system was used to determine the serum concentrations of twenty-four PCB congeners (International Union of Pure and Applied Chemistry number): six dioxin-like (77, 105, 118, 126, 156, and 169) and eighteen non-dioxin like (18, 28, 52, 101, 110, 128, 138, 143, 149, 153, 170, 180, 183, 187, 194, 195, 206, and 209); p,p'-DDT, p,p'-dichlorodiphenyldichloroethane (DDD) and p,p'-DDE; the α, β, and γ isomers of

hexachlorocyclohexane (HCH) and chlordecone. The limit of detection (LD) was 0.05 μg/L for all organochlorine compounds except chlordecone (0.06 μg/L). Detailed information about sampling, analysis, and quality assurance and control has been provided elsewhere (Debier et al. 2003; Multigner et al. 2010). Plasma total cholesterol and total triglyceride concentrations were determined enzymatically (DiaSys Diagnostic Systems GmbH; Holzheim, Germany) and total lipid concentration was calculated as previously described (Bernet et al. 2007).

Statistical analysis

We restricted our analysis to chemicals detected at a rate of more than 80 % (DDE, PCB congeners 138, 153 and 180, and chlordecone) (Table 1). Correlations between concentrations of the frequently detected pollutants were explored by Spearman's rank correlation analysis (see Supplemental Material, Table S1). The concentrations of the various PCBs were highly correlated (Spearman's rho $\geq$0.76, all *p*-values <0.001), so we restricted further analysis to PCB153.

The odds ratio (OR) and 95% confidence intervals (CIs) for the association between PCa and organochlorines according to category of exposure were estimated using unconditional logistic regression. Organochlorines were categorized into quintiles according to the distribution in control subjects. Exposure levels equal to or below the LD were included in the first (lowest) quintile.

Potential confounders were included as covariates in logistic models if they predicted case status (Table 2) and exposure (Supplemental Material, Table S2) with p $\leq$0.05. We also adjusted all models for total lipids (g/L), rather than modeling concentrations of the fat-soluble exposure of interest on a per-unit serum-lipid basis, as the latter approach may be prone to bias (Porta et al.

2009). For each exposure, we also considered the other contaminants as potential confounders. Spearman's rank correlation coefficients between chlordecone and DDE concentrations and between chlordecone and PCB153 concentrations were low (ρ = 0.05 and 0.07 in controls and 0.04 and 0.07 in cases, respectively; Supplemental Material, Table S1). Consequently, chlordecone was not considered as confounder. Next, models of DDE as the primary exposure were adjusted for age (log linearity of age was not achieved and therefore age was categorized as quartiles according to the age distribution of the controls), waist to hip ratio, type 2 diabetes, alcohol, total lipids and PCB153 (quintiles). Models of PCB153 as the exposure were adjusted for the same covariates, plus Caribbean origin and past residence in a Western country, and DDE (quintiles). Sensitivity analyses were conducted including additional adjustment for BMI, PSA screening history, family history of PCa, and chlordecone. Additional sensitivity analyses were realized excluding any subject (n = 199), control or case, with a prediagnostic BMI< 18.5 or $\geq$30.

Missing data for covariates varied from none to 2 (0.2%) for past residence in Western countries and for PSA screening history, 8 (0.6%) for smoking, 20 (1.6%) for alcohol, 27 (2.2%) for family history of PCa, 30 (2.4%) for education, 34 (2.8%) for diabetes, 37 (3.0%) for BMI, and 219 (17.8%) for waist-to-hip-ratio. Missing data were handled by multiple imputations according to the methodology described by Rubin (1987) and Little & Rubin (1987) using chained equations (MICE) (Van Buuren et al. 1999; White et al. 2009). For the imputation procedure, we included the following characteristics: age, Caribbean origin, education, weight, height, waist and hip circumference, smoking, alcohol, diabetes, PSA screening history, family history of PCa, past residence in Western countries, total plasma lipids, all organochlorines, and case - control status. A total of five imputed datasets were generated using 20 cycles per imputation, and the main analyses were repeated using the imputed data. In addition, we performed sensitivity

analyses substituting missing data with a missing value indicator variable, and by doing with complete case analyses restricted to participants with known values of all covariates. Tests for trends were performed by modeling categorical exposures as ordinal variables after assigning median values to each exposure category.

We considered possible interactions between organochlorine exposure and covariates in relation to PCa. The cross-product of covariates (BMI < 25 or ≥ 25 kg/m^2; waist-to-hip-ratio ≤ 0.95 or > 0.95; smoking, never versus former or current; alcohol consumption, never versus former or current; diabetes type 2, yes, no; past residence in Western countries, yes, no; history of PSA screening, yes, no) and exposures (quintiles) were introduced in the logistic model. Subjects with missing values for the factors of interest were excluded from these analyses. We adjusted for the same covariates as the main model for each exposure. Consistent with the recommendations of Seaman et al. (2012), these analyses were restricted to participants with known values of all covariates. The P value for interaction was calculated by the likelihood ratio test comparing the log-likelihood for the model with the interaction terms to the log-likelihood for the model without the interaction term. Interactions with a p-value for the cross-term product ≤ 0.20 were further assessed with stratified analyses.

Polytomous logistic regressions models were used to estimate associations between exposures and case subgroups (versus controls) according to grade (Low grade: Gleason score <7 or 3+4; High grade: Gleason score 4+3 or >7) and clinical stage at diagnosis (Tumour, Nodes, Metastases; localized stage: T1c or T2 and N0 and M0; advanced stage: T3 or T4, or N+ or M+). Exposures were categorized into tertiles according to the distribution in control subjects for theses analyses.

Using previously published data (Multigner et al. 2010), we reanalyzed the association between chlordecone exposure and PCa among participants included in the present analysis, with additional adjustment for plasma DDE and PCB153. After analysis of quality control samples consisting of human plasma spiked with a series of concentrations of chlordecone, we defined the LD for plasma chlordecone concentrations as 0.06 µg/L, rather than using an LD of 0.25 µg/L, as in our previous analysis (Multigner et al. 2010).

SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina) was used for analyses; all tests were two-sided, and P values <0.05 were considered statistically significant.

Results

The results presented here were obtained from a study population comprising 576 of the 709 eligible PCa cases and 655 of the eligible 722 controls, from whom we were able to obtain blood samples and measure plasma organochlorine concentrations. The baseline characteristics of the study population are summarized in Table 2.

The adjusted OR was 1.53 (95% CI 1.02, 2.30) for men in the highest quintile of DDE concentration compared with men in the lowest quintile (Table 3). The relationship between exposure and PCa was significant ($P_{Trend} = 0.01$). This overall trend seems to be mainly driven by the OR for the highest versus lowest quintiles, as the other ORs were close to null. Results of sensitivity analyses were comparable to the primary analysis when missing data were modeled using missing value indicator categories; when we performed complete case analyses; and when BMI, PSA screening history, family history of PCa, or chlordecone exposure were included in the full model (Supplemental Material, Table S3). Excluding subjects with BMI <18.5 and $\geq$30

resulted in a slight decrease in the OR (1.43, 95%CI 0.93, 2.20) but the trend across exposure categories remained significant (P_{Trend} = 0.04) (Supplemental Material, Table S3).

Contrary to what was observed for DDE, adjusted ORs relative to the lowest quintile of PCB 153 concentration all were significantly below 1 (OR = 0.30; 95% CI 0.19, 0.47 for the highest versus lowest quintile) (Table 3). The overall trend for the association across exposure categories was significant (P_{Trend} <0.001). In sensitivity analyses, associations were comparable when missing data were modeled using missing value indicator categories; when restricted to a complete case analysis; and when additionally adjusted for BMI, PSA screening history, family history of PCa, or chlordecone exposure (Supplemental Material, Table S4). Also, exclusion of subjects with BMI <18.5 and ≥30 did not greatly affect the ORs (Supplemental Material, Table S4).

We did not find any evidence of effect modification (interaction p-values > 0.2, data not shown) with the exception of family history of PCa and PCB153 exposure (Supplemental Material, Table S5). Associations between PCB153 exposure and PCa were stronger in men without a family history of PCa, and the interaction terms, although not significant, were ≤ 0.10 for the three highest quintiles of exposure.

Our next analyses considered clinical characteristics. The adjusted OR for cases with high grade Gleason score was 1.92 (95% CI 1.04, 3.54) for men in the highest tertile relative to men in the lowest tertile of DDE concentration (Table 4), but this was not significantly different from the corresponding OR value for cases with low grade ($P_{Heterogeneity}$ = 0.13). For PCB153, a significant inverse association was observed among cases with low grade Gleason score (OR 0.35, 95% CI 0.25, 0.51) for men in the highest tertile relative to men in the lowest tertile (Table 4); this was

significantly different to what was observed for cases with high grade ($P_{Heterogeneity}$ = 0.04). No significant differences were observed between localized and advanced stage of PCa for either DDE or PCB153 exposure.

Finally, we reanalyzed the association between chlordecone exposure and PCa: the OR was 1.65 (95% CI 1.09, 2.48, P_{Trend} = 0.01) for men in the highest quintile compared with men in the lowest quintile (Supplemental Material, Table S6). Comparable results were observed if DDE or PCB153 concentrations were included in the full model (OR 1.64, 95% CI 1.09, 2.47; P_{Trend} = 0.01, and OR 1.70, 95% CI 1.12, 2.56, P_{Trend} = 0.008, respectively) (Supplemental Material, Table S6).

Discussion

In our study population, the highest quintile of exposure to DDE, evaluated by determining plasma p,p'-DDE concentrations, was positively associated with incident PCa. By contrast, plasma PCB153 was inversely associated with PCa, with significant negative associations for all quintiles above the reference level, and the strongest association with the highest quintile.

These results were obtained by studying a population with plasma concentrations consistent with the range of background environmental levels currently found in US populations of similar age (CDC, 2009). The median value for plasma-lipid-adjusted DDE (0.38 µg/g) and PCB153 (0.15 µg/g) in our control population was, for DDE, in the same range as (0.27-0.94 µg/g) and, for PCB153, slightly higher than (0.04-0.09 µg/g) those in control populations in other studies investigating the relationships between these pollutants, determined by blood measurement, and PCa (Aronson et al. 2010; Ritchie et al. 2003, 2005; Sawada et al. 2010; Xu et al. 2010). In the French West Indies, DDT has not been extensively used in agricultural supplies or for disease

vector control. In addition, this territory has had only very limited industrial activities involving significant use or emission of PCBs. Consequently, exposure to these chemical pollutants is likely to be associated with background contamination of the food chain.

To our knowledge, this is the largest study to have investigated associations of DDE and PCBs with PCa based on biological measurements of exposure. Other strengths of this study include its population-based design, the consideration of co-exposure to other organochlorine compounds [and in particular chlordecone which has been found previously to be associated with the risk of PCa (Multigner et al. 2010)], case evaluation and exposure measurement within two months of diagnosis and before treatment, and using multiple imputation to handle missing data.

Our study also suffers some limitations inherent to the case – control design. Factors potentially generating bias must be considered, particularly those relating to differential errors in the measurement of disease or exposure. Case identification was based on unambiguous histological criteria and controls were also selected on the basis of strict criteria, such as normal findings on digital rectal examination and PSA in the normal range for age, taking into account the ethnic background of the population.

The use of DDT and PCBs spread worldwide around the middle of the 20th century, so the study population has probably been exposed to these chemicals or their metabolites throughout much of their lifetimes. Single determinations of plasma organochlorine concentration provide an accurate reflection of the load of this compound in the body and are commonly used as an effective way to determine the extent of chronic exposure to these chemicals. However, questions have been raised about whether a single blood determination of persistent chemicals at the time of cancer diagnosis is a reliable indicator representing lifetime exposure, particularly for

breast cancer (Verner et al. 2011). Nevertheless, unlike women, men are not subject to the mobilization of fat-soluble chemicals during pregnancy or breastfeeding that can significantly alter the pollutant load of the whole body. Any previous weight loss or gain, particularly if substantial, may modify the blood concentration of these pollutants. Unfortunately, we did not collect data for our study population about the gain or loss of body weight during adulthood. To overcome, albeit only in part, this lack of information, we performed a sensitivity analysis by excluding subjects who were underweight or obese: these individuals were, perhaps, the most likely to have changed weight significantly since the beginning of adulthood.

Few studies have investigated relationships between human exposure to DDE and PCBs, determined by blood measurement, and PCa, but all were inconclusive (Aronson et al. 2010; Ritchie et al. 2003, 2005; Sawada et al. 2010; Xu et al. 2010). Nevertheless, Xu et al (2010) reported that ORs for the second and third tertiles of DDE exposure were 2.05 (95% CI, 0.76-5.5) and 2.64 (95% CI 0.92-7.57), respectively. Non-significant inverse associations have been reported between PCBs and PCa in a Canadian case-control study (Aronson et al. 2010) and in a Japanese nested case-control study specifically addressing advanced stage PCa (Sawada et al. 2010). An ecological study in Eastern Slovakia reported a lower incidence of PCa in a district with extensive environmental contamination from a former PCB production site and where residents presented high concentrations of PCBs in blood levels than in a district without any history of PCB production and where residents had low blood concentrations of PCBs (Pavuk et al. 2004).

We investigated whether DDE or PCB153 exposure were associated with PCa aggressiveness. Gleason score and clinical stage at diagnosis are powerful predictors of the aggressiveness of PCa. In particular, patients with high grade Gleason scores have lower metastasis free-survival

and higher PCa-specific mortality. PCB153 exposure appeared to be negatively associated with low grade Gleason score. Screening procedures may introduce distortions in the associations observed between exposures of interest and cancer outcomes if fewer cases would have been included in the absence of screening (Weiss 2003). In our study population, the prevalence of PSA screening among PCa cases with low grade Gleason Score was 76.7% but among PCa cases with high grade, it was only 10%. Also, we found that additional adjustment for PSA screening did not change the risk estimates (data not shown). These various observations suggest that PCB153 exposure may truly decrease the occurrence of low grade PCa without changing the occurrence of high grade forms. Some authors (Koutros et al. 2013) have suggested that the different associations between chemical exposures (i.e. pesticides) and PCa aggressiveness may be consequences of different roles of such exposures in the prostatic carcinogenesis (for example, earlier initiation stage versus prostate cancer progression). However, it has not been established that non aggressive and aggressive forms of PCa are etiologically and pathogenically similar.

Finally, we found that the negative association between PCB153 and PCa was stronger among subjects without a family history of PCa than among those with such a family history. Because the interaction terms were not strictly significant and number of cases with a family history of PCa was very small, these results should be interpreted with caution. This result differs with those reported for various other organochlorine or pesticide exposures: increased risks have been observed among subjects with a family history of PCa, possibly due to genetic susceptibility (Alavanja et al. 2003; Christensen et al. 2010; Lynch et al. 2009; Mahajan et al. 2006; Multigner et al. 2010). Overall, exposure to PCB153 appears to be inversely associated with less aggressive prostate cancer and tends to be most strongly associated among subjects without a family history

of PCa; such patients have a better prognosis than those with a family history (Kupelian et al. 2006).

Mainly on the basis of data from animal experiments, the International Agency for Research on Cancer currently classifies DDT as "possibly carcinogenic to humans" and PCBs (because of their positive association with melanoma in humans) as "probably carcinogenic to humans" (IARC 1991). Both are classified as "reasonably anticipated to be human carcinogens" by the US National Toxicology Program (US NTP 2014). Thus, the observation from this study that PCa is positively associated with DDE, and negatively associated with PCB153 is unexpected; however, these findings may reflect differences in the hormonal properties of DDE and PCB153 and their effects on prostate development, as discussed below.

DDE displays anti-androgenic effects *in vivo*, as assessed from changes in the weights of androgen-responsive tissues (Owens et al. 2007). These effects are probably mediated by competitive binding to the androgen receptor (AR) and/or inhibition of AR-dependent gene expression (Kelce et al. 1995; 1997). In adult healthy subjects without PCa, DDE exposure is negatively associated with serum concentration of dihydrotestosterone (Emeville et al. 2013) suggesting that DDE could also indirectly affect androgen signaling. However, DDE, like many other EDCs, has mixed actions on different members of the steroid receptor superfamily. DDE also exerts agonistic activity on estrogen receptor alpha (ERα) (Li et al (2008). ERα mediates adverse effects of estrogen on the prostate, including aberrant proliferation, inflammation, and malignancy (Ellem & Risbridger 2009). It is therefore difficult to predict the net effect of DDE on the prostate given potential effects on both AR and ERα (Carruba 2007; Ellem & Risbridger 2010).

Unlike dioxin-like PCBs, non-dioxin-like PCBs, which are the most common prevalent PCBs in the environment (McFarland and Clarke 1989), do not interact substantially with the aryl hydrocarbon receptor and may act through different pathways, such as steroid hormone signaling (Cooke et al. 2001). Experimental studies using various animal models have shown that PCB153, the PCB congener most commonly found in animal and human tissues, due to its high persistence and low environmental degradability (Safe 1993) has pro-estrogenic activities (Cooke et al. 2001; Dickerson et al. 2011; Hansen 1998). However, PCBs have also been reported to be anti-estrogenic in both reporter gene and MCF-7 cell proliferation assays (Plísková et al. 2005) and to decrease ER-mediated activity in ER-CALUX bioassays (Oh et al. 2007). Thus, the actions of non-dioxin-like PCBs on ER pathways are complex and depend on the ER subtypes that are being activated or antagonized. Moreover, the non-genomic ER pathways should also be considered. In MCF-7 cells, PCB153 induces the mitogen-activated protein kinase involved in the extracellular signal-regulated kinase (ERK) 1/2 signaling pathways (Radice et al. 2008). Several isothiocyanates from cruciferous vegetables and polyphenols from green or black tea inhibits human PCa cell proliferation (Gupta et al. 2001; Melchini et al. 2013). Interestingly, the antiproliferative effects of these substances seem to be mediated by ERK1/2 phosphorylation (Siddiqui et al, 2004; Melchini et al. 2013). In summary, the modes of action of DDE and ndl PCBs need to be investigated, particularly as involves all the various steroid receptor pathways to improve our understanding of their involvement in the proliferation or inhibition of PCa cells.

More than twenty years after the endocrine disruption concept first emerged (Colborn et al. 1993), this issue is still the subject of debate (Bergman et al. 2013; Dietrich et al. 2013; Gore et al. 2013). For instance, it has been reported that some EDCs have unexpected and potent effects

at very low doses and/or do not generate the standard monotonic dose response curves seen for other types of compounds (Fagin 2012). Whether the interplay between different receptor mechanisms can generate unusual dose-response relationships and/or explains the associations we estimated for PCB153 remains to be elucidated.

Caution is required in the interpretation of our findings. The possibility that our findings were confounded by unmeasured exposures or could be explained by reverse causality cannot be excluded. However, the possible influence, if any, of PCa on organochlorine concentrations in blood remains to be studied, and nothing is known about any underlying mechanism. Also, we cannot exclude the possibility that our findings, particularly for PCBs, may have resulted from selection bias associated with uncontrolled or unmeasured common causes of competing outcomes of PCB-related diseases and PCa (Thompson et al. 2013).

Conclusions

In our study population of men of African descent from the French West Indies, DDE exposure was positively associated with PCa whereas PCB153 exposure was negatively associated with PCa. PCB153 exposure was also inversely associated with less aggressive forms of the disease. These contrasting associations may be related to the different and sometimes multiple modes of hormonal action attributed to these two classes of pollutants. Our findings add complexity to the already controversial issue of EDCs and their suspected effects on human health. Replication of these observations in other populations, and mechanistic studies, are needed before any causal link can be established.

References

Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF et al. 2003. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. Am J Epidemiol 157:800-814.

Aronson KJ, Wilson JW, Hamel M, Diarsvitri W, Fan W, Woolcott C et al. 2010. Plasma organochlorine levels and prostate cancer risk. J Expo Sci Environ Epidemiol 20:434-445.

Bergman Å, Andersson AM, Becher G, van den Berg M, Blumberg B, Bjerregaard P et al. 2013. Science and policy on endocrine disrupters must not be mixed: a reply to a "common sense" intervention by toxicology journal editors. Environ Health 12:69

Bernert JT, Turner WE, Patterson DG Jr, Needham LL.2007. Calculation of serum "total lipid" concentrations for the adjustment of persistent organohalogen toxicant measurements in human samples. Chemosphere 68:824-831.

Carruba G. 2007. Estrogen and prostate cancer: an eclipsed truth in an androgen-dominated scenario. Cell Biochem 102: 899-911.

Christensen CH, Platz EA, Andreotti G, Blair A, Hoppin JA, Koutros S, et al. 2010. Coumaphos exposure and incident cancer among male participants in the Agricultural Health Study (AHS).

Environ Health Perspect 118:92-96.

Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O et al. 2012. International variation in prostate cancer incidence and mortality rates. Eur Urol 61:1079-1092

CDC [Centers for Disease Control and Prevention]. 2009. Fourth Report on Human Exposure to Environmental Chemicals. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Available: http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf [accessed 11 November 2014].

Colborn T, vom Saal FS, Soto AM. 1993. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 101:378-384

Cooke PS, Sato T, Buchanan DL. 2001. Disruption of steroid hormone signaling by PCBs. In: recent Advances in Environmental Toxicology and Health effects (Robertson LW, Hansen LG, eds). Lexington, KY: University press of Kentucky, 257-263.

Damber JE, Aus G. 2008. Prostate cancer. Lancet 371:1710-1721.

Debier C, Pomeroy PP, Dupont C, Joiris C, Comblin V, Le Boulengé E et al. 2003. Quantitative dynamics of PCB transfer from mother to pup during lactation in UK grey seals Halichoerus grypus. Mar Ecol Prog Ser 247:237–248.

Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM et al. 2009. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 30:293-342.

Dickerson SM, Cunningham SL, Patisaul HB, Woller MJ, Gore AC. 2011. Endocrine disruption of brain sexual differentiation by developmental PCB exposure. Endocrinology 152:581-594.

Dietrich DR, Aulock Sv, Marquardt H, Blaauboer B, Dekant W, Kehrer J, et al. 2013. Scientifically unfounded precaution drives European Commission's recommendations on EDC regulation, while defying common sense, well-established science and risk assessment principles. Chem Biol Interact 205:A1-5.

Ellem SJ, Risbridger GP. 2009. The dual, opposing roles of estrogen in the prostate. Ann N Y Acad Sci 1155: 174-186.

Ellem SJ, Risbridger GP. 2010. Aromatase and regulating the estrogen:androgen ratio in the prostate gland. J Steroid Biochem Mol Biol 118: 246-251.

Emeville E, Giton F, Giusti A, Oliva A, Fiet J, Thomé JP et al. 2013. Persistent organochlorine pollutants with endocrine activity and blood steroid hormone levels in middle-aged men. PLoS One 8:e66460.

Fagin D. The learning curve. 2012. Nature 490:462-465

Gore AC, Balthazart J, Bikle D, Carpenter DO, Crews D, Czernichow P et al. 2013. Policy decisions on endocrine disruptors should be based on science across disciplines: a response to Dietrich et al. Endocrinology 154:3957-3960.

Gupta S, Hastak K, Ahmad N, Lewin JS, Mukhtar H. 2001. Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols. Proc Natl Acad Sci U S A 98: 10350-10355. Hansen LG. 1998. Stepping backward to improve assessment of PCB congener toxicities. Environ Health Perspect 106 S1:171-89.

Hsing AW, Chokkalingam AP. 2006. Prostate cancer epidemiology. Front Biosci 11:1388-1413.

IARC [International Agency for Research on Cancer]. 1991. Working group on the evaluation of the carcinogenic risk of chemicals to humans. Occupational exposures in insecticide application, and some pesticides. IARC monographs on the evaluation of carcinogenic risks to humans, volume 53. Lyon, France: International Agency for Research on Cancer, World Health Organization, 179–250

Kelce WR, Stone CR, Laws SC, Gray LE, Kemppainen JA, Wilson EM. 1995. Persistent DDT metabolite pp'-DDE is a potent androgen antagonist. Nature 376:581-585.

Kelce WR, Lambright CR, Gray LE Jr, Roberts KP.1997. Vinclozolin and p,p'-DDE alter androgen-dependent gene expression: in vivo confirmation of an androgen receptor-mediated mechanism. Toxicol Appl Pharmacol 142:192-200.

Koutros S, Beane Freeman LE, Lubin JH, Heltshe SL, Andreotti G, Barry KH, et al. 2013. Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study. Am J Epidemiol 177:59-74.

Kupelian PA, Reddy CA, Reuther AM, Mahadevan A, Ciezki JP, Klein EA. 2006. Aggressiveness of Familial Prostate Cancer. J Clin Oncol 24: 3445-3450.

Li J, Li N, Ma M, Giesy JP, Wang Z. 2008. In vitro profiling of the endocrine disrupting potency of organochlorine pesticides. Toxicol Lett 183:65-71.

Little RJA, Rubin DB. 1987. Statistical Analysis with Missing Data. New York, NY: John Wiley & Sons.

Lynch SM, Mahajan R, Beane Freeman LE, Hoppin JA, Alavanja MC. 2009. Cancer incidence among pesticide applicators exposed to butylate in the Agricultural Health Study (AHS). Environ Res 109:860-868.

Mahajan R, Bonner MR, Hoppin JA, Alavanja MC. 2006. Phorate exposure and incidence of cancer in the Agricultural Health Study. Environ Health Perspect 114:1205-1209.

McFarland VA, Clarke JU. 1989. Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis. Environ Health Perspect 81:225-329.Melchini A, Traka MH, Catania S, Miceli N, Taviano MF, Maimone P et al. 2013. Antiproliferative activity of the dietary isothiocyanateerucin, a bioactive compound from cruciferous vegetables, on human prostate cancer cells. Nutr Cancer 65:132-138.

Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, Moul JW. 1996. Age-specific reference ranges for prostate-specific antigen in black men. N Engl J Med 335:304-310.

Multigner L, Ndong JR, Giusti A, Romana M, Delacroix-Maillard H, Cordier S et al. 2010. Chlordecone exposure and risk of prostate cancer. J Clin Oncol 28:3457-3462.

Oh SM, Ryu BT, Lee SK, Chung KH. 2007. Antiestrogenic potentials of ortho-PCB congeners by single or complex exposure. Arch Pharm Res 30:199-209.

Owens W, Gray LE, Zeiger E, Walker M, Yamasaki K, Ashby J et al. 2007. The OECD program to validate the rat Hershberger bioassay to screen compounds for in vivo androgen and antiandrogen responses: phase 2 dose-response studies. Environ Health Perspect 115:671-678.

Pavuk M, Cerhan JR, Lynch CF, Schecter A, Petrik J, Chovancova J et al. 2004. Environmental exposure to PCBs and cancer incidence in eastern Slovakia. Chemosphere 54:1509-1520.

Plísková M, Vondrácek J, Canton RF, Nera J, Kocan A, Petrík J et al. 2005. Impact of polychlorinated biphenyls contamination on estrogenic activity in human male serum. Environ Health Perspect 113:1277-1284

Porta M, Jariod M, López T, Pumarega J, Puigdomènech E, Marco E et al. 2009. Correcting serum concentrations of organochlorine compounds by lipids: alternatives to the organochlorine/total lipids ratio. Environ Int 35:1080-1085.

Prins GS. 2008. Endocrine disruptors and prostate cancer risk. Endocr Relat Cancer 15:649-656.

Radice S, Chiesara E, Fucile S, Marabini L. 2008. Different effects of PCB101, PCB118, PCB138 and PCB153 alone or mixed in MCF-7 breast cancer cells. Food ChemToxicol 46:2561-2567.

Ritchie JM, Vial SL, Fuortes LJ, Guo H, Reedy VE, Smith EM. 2003. Organochlorines and risk of prostate cancer. J Occup Environ Med 45:692-702.

Ritchie JM, Vial SL, Fuortes LJ, Robertson LW, Guo H, Reedy VE et al. 2005. Comparison of proposed frameworks for grouping polychlorinated biphenyl congener data applied to a case-control pilot study of prostate cancer. Environ Res 98:104-113.

Rubin DB. 1987. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc.

Safe S. 1993.Toxicology, structure-function relationship, and human and environmental health impacts of polychlorinated biphenyls: progress and problems. Environ Health Perspect 100: 259-268.

Sawada N, Iwasaki M, Inoue M, Itoh H, Sasazuki S, Yamaji T et al. 2010. Plasma organochlorines and subsequent risk of prostate cancer in Japanese men: a nested case-control study. Environ Health Perspect 118:659-665.

Seaman SR, Bartlett JW, White JR. 2012. Multiple imputation of missing covariates with non-linear effects and interactions: an evaluation of statistical methods. BMC Med Res Methodol 12:46.

Siddiqui IA, Adhami VM, Afaq F, Ahmad N, Mukhtar H. 2004. Modulation of phosphatidylinositol-3-kinase/protein kinase B- and mitogen-activated protein kinase-pathways by tea polyphenols in human prostate cancer cells. J Cell Biochem 91:232-242.Soto AM, Sonnenschein C. 2010. Environmental causes of cancer: endocrine disruptors as carcinogens. Nat Rev Endocrinol 6:363-370.

Thompson CA, Zhang ZF, Arah OA. 2013. Competing risk bias to explain the inverse relationship between smoking and malignant melanoma. Eur J Epidemiol 28:557-567.

US NTP [US National Toxicology Programme]. 2014. Report on Carcinogens, Thirteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. Available: http://ntp.niehs.nih.gov/go/roc13 [accessed 11 November 2014].

Van Buuren S, Boshuizen HC, Knook DL. 1999. Multiple imputation of missing blood pressure covariates in survival analysis. Statist Med 18:681–694.

Verner MA, Bachelet D, McDougall R, Charbonneau M, Guénel P, Haddad S. 2011. A case study addressing the reliability of polychlorinated biphenyl levels measured at the time of breast cancer diagnosis in representing early-life exposure. Cancer Epidemiol Biomarkers Prev 20:281-286.

Weiss NS. 2003. Adjusting for screening history in epidemiologic studies of cancer: Why, when, and how to do it. Am J Epidemiol 157:957-961.

White IR, Royston P, Wood AM. 2009. Multiple imputation using chained equations: Issues and guidance for practice. Statist Med 30:377-399.

WHO [World Health Organization]. 2013. State of the science of endocrine disrupting chemicals 2012. Ed Bergman A, Heindel JJ, Jobling S, Kidd KA, Zoeller RT. Available: http://unep.org/pdf/9789241505031_eng.pdf [accessed 11 November 2014].

Xu X, Dailey AB, Talbott EO, Ilacqua VA, Kearney G, Asal NR. 2010. Associations of serum concentrations of organochlorine pesticides with breast cancer and prostate cancer in U.S. adults. Environ Health Perspect 118:60-66.

Table 1. Detection and concentrations of organochlorine pollutants in plasma samples from the study population [μg/L (μg/g lipids)].

Organochlorine[a]	Detection frequency (%)	10th percentile	25th percentile	50th percentile	75th percentile	Max
Controls						
p,p'- DDT	36.2	<LD	<LD	<LD	0.07 (0.01)	1.7 (0.32)
p,p'- DDD	24.0	<LD	<LD	<LD	0.04 (0.008)	0.84 (0.15)
p,p'- DDE	96.2	0.39 (0.07)	0.98 (0.18)	2.06 (0.38)	4.37 (0.75)	27.8 (6.7)
PCB28	54.5	<LD	<LD	0.07(0.01)	0.28 (0.05)	8.0 (1.4)
PCB52	42.6	<LD	<LD	<LD	0.28 (0.05)	12.7 (2.5)
PCB101	52.1	<LD	<LD	0.05 (0.009)	0.13(0.02)	1.1(0.21)
PCB118	59.2	<LD	<LD	0.08 (0.01)	0.20 (0.03)	3.3 (0.9)
PCB138	97.4	0.18 (0.03)	0.31 (0.06)	0.53 (0.10)	0.90 (0.16)	12.2 (2.4)
PCB153	98.2	0.24 (0.05)	0.48 (0.09)	0.85 (0.15)	1.47 (0.26)	16.5 (3.5)
PCB180	97.4	0.23 (0.04)	0.39 (0.07)	0.64 (0.12)	1.03 (0.18)	10.3 (2.0)
α - HCH	35.9	<LD	<LD	<LD	0.08 (0.01)	1.6 (0.32)
β - HCH	43.5	<LD	<LD	<LD	0.09 (0.02)	1.9 (0.30)
γ - HCH	27.7	<LD	<LD	<LD	0.08 (0.01)	1.8 (0.41)
Chlordecone	84.1	<LD	0.17 (0.03)	0.42 (0.08)	0.83 (0.15)	49.2 (8.8)
Cases						
p,p'- DDT	29.3	<LD	<LD	<LD	0.06 (0.01)	2.5 (0.43)
p,p'- DDD	20.1	<LD	<LD	<LD	0.03 (0.006)	0.99 (0.15)
p,p'- DDE	95.5	0.40 (0.08)	1.11 (0.22)	2.55 (0.50)	5.74 (1.07)	40.1 (6.6)
PCB28	52.6	<LD	<LD	0.06 (0.01)	0.29 (0.05)	6.8 (1.1)
PCB52	49.3	<LD	<LD	<LD	0.38 (0.07)	6.7 (1.1)
PCB101	51.2	<LD	<LD	0.05 (0.009)	0.13 (0.02)	1.2 (0.17)
PCB118	62.0	<LD	<LD	0.08 (0.02)	0.18 (0.03)	2.4 (0.52)
PCB138	97.9	0.17 (0.03)	0.30 (0.06)	0.54 (0.10)	0.87 (0.18)	6.7 (1.1)
PCB153	98.8	0.23 (0.04)	0.41 (0.06)	0.78 (0.10)	1.24 (0.18)	8.4 (1.3)
PCB180	97.2	0.25 (0.05)	0.37 (0.07)	0.62 (0.12)	0.90 (0.18)	6.2 (1.0)
α - HCH	28.5	<LD	<LD	<LD	0.05 (0.01)	1.2 (0.20)
β - HCH	38.0	<LD	<LD	<LD	0.11 (0.02)	2.2 (0.46)
γ - HCH	18.4	<LD	<LD	<LD	<LD	0.65 (0.13)
Chlordecone	82.8	<LD	0.18 (0.03)	0.43 (0.08)	0.94 (0.18)	26.4 (4.1)

LD: Limit of detection.

[a]PCB congeners 18, 77, 101, 105, 110, 126, 128, 143, 149, 156, 169, 170, 183, 187, 194, 195, 206, and 209 were below the LD in all cases and controls.

Table 2. Baseline characteristics of the study population.

Characteristics	**Cases No. (%)**	**Controls No. (%)**	**P-value** [a]
Age, mean and range (years)	65.9 (52.6 – 79.1)	60.9 (48.0 – 77.1)	<0.001
Caribbean origin			
French West Indies	556 (96.5)	598 (91.3)	<0.001
Haiti or Dominica	20 (3.5)	57 (8.7)	
Education			
Primary	349 (61.0)	362 (57.5)	0.04
Secondary	147 (25.7)	201 (32.0)	
High school and higher	76 (13.3)	66 (10.5)	
Missing data	4	26	
Body mass index (kg/m²)			
< 25	241 (44.5)	306 (46.9)	0.54
25 - < 30	240 (44.3)	268 (41.1)	
≥ 30	61 (11.2)	78 (12.0)	
Missing data	34	3	
Waist-to-hip-ratio			
≤ 0.95	196 (54.4)	455 (69.8)	<0.001
> 0.95	164 (45.6)	197 (30.2)	
Missing data	216	3	
Smoking			
Never	355 (62.2)	410 (62.9)	0.80
Former or current	216 (37.8)	242 (37.1)	
Missing data	5	3	
Alcohol consumption			
Never	74 (13.0)	112 (17.4)	0.03
Former or current	494 (87.0)	536 (82.6)	
Missing data	8	12	
Type 2 diabetes			
No	457 (81.5)	556 (87.4)	0.004
Yes	104 (18.5)	80 (12.6)	
Missing data	15	19	
Past residence in Western countries			
No	403 (70.0)	498 (76.3)	0.01
Yes	173 (30.0)	155 (23.7)	
Missing data	-	2	
PSA screening history			
No	278 (48.4)	572 (87.3)	<0.001
Yes	296 (51.6)	83 (12.7)	
Missing data	2	-	
Family history of prostate cancer			
No	317 (55.9)	498 (78.2)	<0.001
Yes	144 (25.4)	66 (10.4)	
Do not know	106 (18.6)	74 (11.4)	
Missing data	9	18	
Gleason score			
< 7 or 3 + 4	462 (82.1)	-	
> 7 or 4 + 3	101(17.9)	-	
Missing data	9		

Characteristics	Cases No. (%)	Controls No. (%)	P-value [a]
Clinical stage, TNM			
T1c or T2 and N0 and M0	485 (87.4)	-	
T3 or T4, or N+ or M+	70 (12.6)	-	
Missing data	21		

[a]P values were calculated using a two-sided Chi2 test for a comparison of percentages or by a two-sided Student's *t* test for a comparison of means.

Table 3. ORs (95% CIs) of prostate cancer according to quintile of DDE and PCB 153 exposure.

Exposure (µg/L)	No. Controls	No. Cases	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
DDE (µg/L)				
<0.79	131	106	1.0	1.0
0.79-1.62	130	96	0.91 (0.63, 1.62)	0.96 (0.66, 1.42)
1.63-2.89	133	111	1.03 (0.72, 1.48)	1.05 (0.71, 1.55)
2.90-5.18	131	104	0.98 (0.68, 1.41)	1.02 (0.67, 1.53)
≥5.19	130	159	1.51 (1.07, 2.13)	1.53 (1.02, 2.30)
P_{Trend}			0.003	0.01
PCB153 (µg/L)				
<0.41	132	141	1.0	1.0
0.41-0.69	132	109	0.77 (0.55, 1.09)	0.56 (0.38, 0.83)
0.70-1.07	134	135	0.94 (0.67, 1.32)	0.67 (0.46, 0.99)
1.08-1.70	131	110	0.79 (0.55, 1.11)	0.45 (0.30, 0.63)
≥1.71	126	81	0.60 (0.42, 0.87)	0.30 (0.19, 0.47)
P_{Trend}			0.01	< 0.001

[a]For DDE: Adjusted for age, waist-to-hip-ratio, type 2 diabetes, alcohol, total plasma lipid concentration and PCB153. For PCB153: Adjusted for age, waist-to-hip-ratio, Caribbean origin, past residence in western countries, type 2 diabetes, total plasma lipid concentration, alcohol and DDE. Missing values were imputed using a Multiple Imputation by Chained Equation (MICE) approach in five datasets.

Table 4. OR (95% CIs) for DDE and PCB153, and prostate cancer by Gleason score and clinical stage.

Exposure	No. controls	No. low grade	Low grade OR[a] (95% CI)	No. high grade	High grade OR[a] (95% CI)	P Value[b]	No. localized	Localized OR[a] (95% CI)	No. advanced	Advanced OR[a] (95% CI)	P Value[c]
DDE (µg/L)											
<1.37	218	144	1.0	20	1.0		145	1.0	15	1.0	
1.37-3.41	218	151	1.06 (0.77, 1.47)	34	1.55 (0.85, 2.85)	0.23	160	1.11 (0.81, 1.52)	23	1.44 (0.69, 2.98)	0.50
≥3.42	219	167	1.18 (0.84, 1.65)	47	1.92 (1.04, 3.54)	0.13	180	1.26 (0.91, 1.76)	32	1.39 (0.66, 2.93)	0.83
P_{Trend}			0.33		0.06			0.18		0.55	
PCB153 (µg/L)											
<0.60	218	183	1.0	28	1.0		181	1.0	22	1.0	
0.61-1.24	216	174	0.78 (0.57, 1.06)	39	1.11 (0.63, 1.95)	0.22	189	0.83 (0.61, 1.14)	23	0.84 (0.42, 1.68)	0.97
≥ 1.25	221	105	0.35 (0.25, 0.51)	34	0.69 (0.37, 1.29)	0.04	115	0.38 (0.27, 0.55)	25	0.64 (0.30, 1.35)	0.19
P_{Trend}			<0.001		0.10			<0.001		0.28	

[a]For DDE: Adjusted for age, waist-to-hip-ratio, alcohol, type 2 diabetes, total plasma lipid concentration and PCB153. For PCB153: Adjusted for age, waist-to-hip-ratio, Caribbean origin, past residence in western countries, diabetes type 2, total plasma lipid concentration, alcohol and DDE. Missing values were imputed using a Multiple Imputation by Chained Equation (MICE) approach in five datasets. [b]P from the Wald test for heterogeneity of respective β coefficients between low grade and high grade prostate cancer. [c]P from the Wald test for heterogeneity of respective β coefficients between localized and advanced stage prostate cancer.